Determination of Protionamide in Pharmaceutical by Spectrophotometry through Oxidation Reaction with Oxone

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The developed method is based on the oxidation of Protionamide (PTA) by $KHSO_5$ in HCl medium, and absorbance of the obtained PTA–SO is measured at 380 nm. Different variables affecting the reaction were carefully studied and optimized. Beer's law is obeyed in the concentration range of 5 – 45 μg mL^{-1} with the respective molar absorptivity (ε) value of 4920±429 M^{-1} cm^{-1}. The limits of detection and quantification were calculated to be 0.17 and 0.51 μg mL^{-1}, respectively. Precision and accuracy of the method were evaluated by replicate analyses of the pure drug solution at three concentration levels within the linear range. The precision was satisfactory with the RSD values <1.13%. The accuracy of the method, expressed as relative error (% RE), was better than -1.6, revealing fair precision and accuracy of the method. Results of determination of PTA in tablets by the proposed method are in agreement with those obtained by the standard pharmacopoeia method.

Keywords: prothionamide, spectrophotometry, oxone

Визначення протіонаміду у фармацевтичному препараті методом спектрофотометрії за реакцією окиснення з оксоном

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Розроблений метод заснований на окисненні протіонаміду (ПТА) $KHSO_5$ у середовищі HCl, з подальшим вимірюванням світлопоглинання утвореного ПТА-SO за довжини хвилі 380 нм. Умови перебігу реакції ретельно вивчено та оптимізовано. Закон Бера виконується в інтервалі концентрацій 5–45 мкг/мл з відповідним значенням молярного коефіцієнта поглинання (ε) 4920± 429 $M^{-1}·см^{-1}$. Межі виявлення та кількісного визначення становлять 0,17 та 0,51 мкг/мл відповідно. Точність і правильність методу оцінювали шляхом аналізу чистих розчинів лікарського засобу з трьома різними концентраціями в межах лінійного діапазону. Точність отриманих результатів була задовільною зі значеннями RSD<1,13%. Правильність методу, виражена як відносна похибка (%RE), була кращою за –1,6, що свідчить про задовільну відтворюваність результатів. Результати визначення ПТА в пігулках запропонованим методом узгоджуються з результатами, отриманими стандартним фармакопейним методом. Надійність отриманих результатів вимірювань доведена шляхом порівняння прийнятого референтного значення (μ) з результатами, отриманими запропонованим методом: $|(\bar{x}-\mu)100\% / \mu| < t\alpha(0,95, n=3) \times RSD/\sqrt{n}$. Також проведено експерименти щодо ступеня відтворення з використанням метода добавок. Відносна похибка (% RE), була кращою за –1,8%; правильність була задовільною з $RSD<1,0\%$: $|(\bar{x}-\mu)100\% / \mu| < t\alpha(P=0,95, n=3) \times RSD/\sqrt{n}$, μ – істинний вміст доданих речовин (мкг/мл), що свідчить про відсутність впливу допоміжних речовин на результати визначення протіонаміду запропонованим методом.

Keywords: протіонамід, спектрофотометрія, оксон

Introduction

Tuberculosis still affects a large number of the world's population and drug resistance is becoming an increasing problem. Second line of defense antitubercular agents such as Protionamide (PTA) are thus becoming increasingly important. Protionamide is a thioamide derivative [1]. Prothionamide is official in The International Pharmacopoeia, Twelfth Edition [2], Indian Pharmacopoeia, (2007) [3], Japan Pharmacopoeia, 2011 [4]. The International Pharmacopoeia for the determination of PTA in tablets proposed High-performance liquid chromatography (HPLC) [2]. According to Chinese Pharmacopoeia, titration method is used for PTA determination, which suffers from low sensitivity [5].

Literature survey reveals that UV spectrophotometric method was developed and validated for the quantitative determination of Prothionamide in bulk drug and in pharmaceutical formulations. Prothionamide shows the maximum absorbance at 288 nm in phosphate buffer (pH 7.4). Prothionamide follows Beer's law in the concentration range of 4-20 μg mL^{-1}. The detection limit (LOD) and quantitation limit (LOQ) were 0.40 and 1.23 μg mL^{-1}, respectively [6].

In order to establish compliance with the requirements of the documentation of the manufacturer of prothionamide tablets, the method of HPLC was used for the quantitative determination of the content of the main substance and accompanying impurities [7].

The method of UV spectroscopy is the most interesting instrumental analytical method, which is widely used for the analysis of pharmaceutical products, because it is a simple, easy, less time-consuming and economical method. There is no other UV spectrophotometric method for the estimation of prothionamide in tablets. Consequently, it was deemed necessary to develop a UV spectrophotometric method that does not use complexing agents and harmful chemicals, extraction or evaporation steps. It was proposed that as Protionamide is oxidized, there may be a shift in its absorbance spectrum.

Potassium peroxomonosulfate is used in quantitative analysis for various pharmaceutical groups. The substance has high oxidation activity accompanied with high stability that makes a great value development of new procedures using potassium peroxomonosulfate as oxidation reagent. It is commercially available and costefficient. An intensive scientific work describes application of potassium peroxomonosulfate in spectrophotometry, fluorimetry and voltammetry for analysis of antibiotics (penicillins and cephalosporins), derivatives of phenothiazine, alkaloids, esters and peroxides [8].

The aim of this work was to develop easy, rapid, and reliable method based on oxidation reaction employing potassium peroxomonosulfate which finds extensive application in spectrophotometric assay of pharmaceuticals.

Experimental part

Reagents and instruments

Apparatus

A double–beam UV-Visible spectrophotometer, model – UV1800 (Shimadzu, Japan), UV-Probe 2.62 software with matched 1-cm quartz cells was used for absorbance measurements. The kinetics of oxidation of Protionamide, using potassium peroxomonosulfate in slightly acidic media were studied by spectrophotometric techniques.

All melting points were determined with Polmon melting point apparatus.

Fourier Transform Infrared (FT-IR) Spectral Analysis. Samples were scanned at the functional group region (4000–650 cm^{-1}) using a Shimadzu FT-IR spectrometer (Shimadzu, Kyoto, Japan). Tablets were prepared by mixing 200 mg of potassium bromide and 2 mg of the test compound (1% concentration) followed by compression in the standard manner.

^{1}H-NMR spectra were recorded on a Bruker 300 spectrometer. Chemical shifts are reported in ppm downfield from TMS as internal standard.

Elemental analyses were performed using a Heraeus CHN-O-Rapid instrument.

Preparation of oxidation PTA *product* (PTA-SO). Prothionamide sulphoxide was prepared by oxidation of the parent thioamide by $KHSO_5$ as the triple salt $2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$ (Oxone) in HCl solution medium. Prothionamide (1.8 g, 0.01 moL) and triple salt $2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$ (Oxone) (3 g, 0.01 moL $KHSO_5$) dissolved in 0.05 M HCl (100 mL) mixture was stirred for 10 min at 25°C, extract the product with dichloromethane (100 mL), concentrated, isolated with hexane(50 mL) to yield 7 (1.47 g, 75%) as a yellow solid (mp 112-114°C); Prothionamide sulfoxide was purified three times by recrystallization from dichloromethane/hexane (1:1 v/v); mp 119-121°C; IR (KBr, cm^{-1}) 2953, 1637, 1599, 1532, 1482, 1406, 1307, 1232, 1136, 976, 933, 807 and 711; ^{1}H-NMR (300 MHz, DMSO) d 0.89 (t, 3H, *J* 7.5 Hz), 1.70 (m, 2H), 2.72 (t, 2H, *J* 7.5 Hz), 7.30 (d, 1H, *J* 4.8 Hz), 8.55 (d, 1H, *J* 5.1 Hz), 7.37 (s, 1H), 8.49 (s, 1H), 9.39 (s, 1H). Anal. Calcd. For $C_9H_{12}N_2OS$ (196.27): C, 55.08; H, 6.16; N, 14.27; O, 18.15; S, 16.34. Found: C, 55.06; H, 6.15; N, 14.30; O, 18.16; S, 16.33.

Major principle peaks of aromatic stretching, N-H stretching, C-N stretching, C=S stretching, =C-H bending were observed for pure Prothionamide at 2931, 1596, 1289, 1150 and 901 cm^{-1} respectively. The IR spectrum of PTA-SO shows the same bands of PTA (2953, 1599, 1306, 1136 and 933 cm^{-1} respectively), indicating that no changes had occurred to the peripheral amide link, besides the appearance of a new band at about 1232 cm^{-1} showing the formation of a new sulfoxide group due to oxidation (Fig. 1).

Preparation of oxidation PTA product 2-Propyl-isonicotinamide. 2-Propylisonicotinamide was obtained according to the same method as Prothionamide sulfoxide, with the difference that

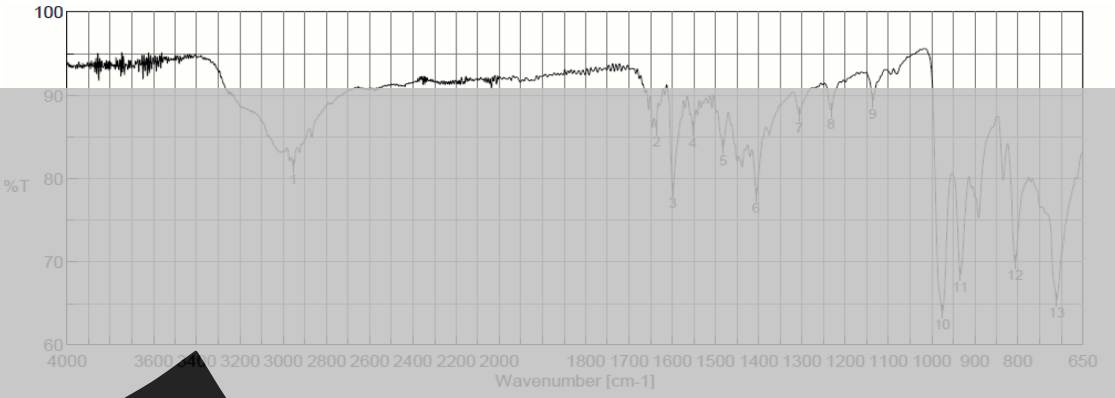

Fig. 1. The FT-IR spectrum of PTA-SO.

the oxidant was taken in a two-fold molar excess in relation to the amount of Prothionamide taken, and the reaction time was 2 hours.

2-Propylisonicotinamide as a almost white solid substance, mp 124-130°C (Lit. 125-130°C [9]; IR (KBr, cm^{-1}) 3350, 2360, 1675, 1550, 1421. Anal. Calcd. For $C_9H_{11}NO_2$ (164.20): C, 65.43; H, 6.71; N, 8.50; O, 19.39. Found: C, 65.42; H, 6.70; N, 8.49; O,19.39.

Materials and reagents

All reagents and solvents employed were of commercial grade and were used as such, unless otherwise specified. Doubly distilled water was used. A 0.7% aqueous solution of $KHSO_5$ (Oxone®, Acros Organics) was prepared in the usual manner. Potassium peroxomonosulfate is widely used as an oxidizing agent (usually referred to as monopersulfate or "MPS"). It is the potassium salt of peroxymonosulfuric acid. Usually potassium peroxomonosulfate is available as the triple salt $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$, known as Oxone. Oxone has a longer shelf life than does potassium peroxomonosulfate. A white, water-soluble solid, Oxone loses <1% of its oxidizing power per month [10]. The standard electrode potential for potassium peroxomonosulfate is +1.81 V (pH = 0) with a half reaction generating the hydrogen sulfate:

$$HSO_5^- + 2H^+ + 2e^- \rightarrow HSO_4^- + H_2O.$$

Pure Protionamide (PTA) sample certified to be 98.9% pure was provided from LGC GmbH (Germany) and used as received.

A 500 μg mL^{-1} standard solution of PTA was prepared by dissolving 250 mg of pure drug in 0.05 M HCl and diluted with the same solvent in a 500 mL volumetric flask.

Protionamide 250 mg film-coated tablets № 50, (Lupin Ltd, India), TB206. *List of excipients*: *Core tablet:* colloidal silicon dioxide, corn (maize) starch, dibasic calcium phosphate, dihydrate magnesium stearate, microcrystalline cellulose, povidone, propylene glycol, sodium benzoate, sodium starch glycolate, talc. *Film coat*: hypromellose, lake of quinoline yellow, polyethylene glycol, talc, titanium dioxide. Protionamide 250 mg film-coated tablets contains NLT 95.0% and NMT 105.0% of the labeled amount of Protionamide ($C_9H_{12}N_2S$) .

Stoichiometric determinations were carried out by mixing various ratios of Protionamide and $KHSO_5$ in tightly sealed volumetric flasks and scanning them spectrophotometrically for depletion of $KHSO_5$ over periods of up to 24 h. Excess $KHSO_5$ could be determined by adding excess acidified iodide and back-titrating with standard thiosulfate using freshly prepared starch as indicator.

$$KHSO_5 + 2I^- + 2H^+ \rightarrow KHSO_4 + I_2 + H_2O$$

The 0.7% aqueous solution of $KHSO_5$ was used as a reagent. The solution was prepared using volume-mass method. The precise weight 0.7 g of Oxone was dissolved in 100 mL of double-distilled water. The exact amount of $KHSO_5$ was determined by the method of iodometric titration.

General procedures

Construction of a calibration graph

Varying aliquots (0.25–2.25 mL) of standard 500 μg mL^{-1} PTA solution were accurately transferred into a series of 25 mL volumetric flasks, and the volume was diluted to 3 mL with 0.05 HCl. To each flask 0.25 mL of 0.7% aqueous solution of $KHSO_5$ was added successively, the volume was then made up to the mark with water, mixed well, and absorbance measured at 360 nm versus the reagent blank every 30 seconds for 3 minutes. Absorbance at the time of 0 s after mixing the solutions for a given concentration of prothionamide was determined by extrapolation of the resulting falling kinetic curve to the intersection with the "Abs" axis.

6 Point calibration curve data was constructed in the range of 5 to 45 μg mL^{-1}, where the Beer's law was obeyed. The unknown concentration was calculated using a regression equation from the obtained absorbance data.

Procedure for tablets

Twenty tablets were weighed accurately and ground into a fine powder. A portion of the powder equivalent to 250 mg of PTA was weighed accurately and transferred into a 500 mL volumetric flask, 250 mL of 0.1 M HCl was added, and the content was shaken for 20 min. The volume was diluted to

the mark with doubly distilled water, mixed well, and filtered using Whatman 42 filter paper. The filtrate (500 μg mL^{-1} in PTA) was analyzed using 0.50 mL, 0.75 mL and 1.00 mL according to the method, in five replicates: the indicated volumes of the filtrate solution were accurately transferred to a 25 mL volumetric flask and the volume was made up to 3 mL with 0.05 HCl. Same procedure as mentioned in the general procedures for determination of PTA in pure preparation was repeated.

Procedure for placebo

Mixture Analyses

A placebo blank of the composition: colloidal silicon dioxide - 3.5 mg, corn (maize) starch - 3.3 mg, dibasic calcium phosphate - 15 mg, dihydrate magnesium stearate - 2 mg, microcrystalline cellulose - 38.5 mg, lactose monohydrate - 14.5 mg ,povidone - 5 mg, propylene glycol - 5 mg , sodium benzoate - 0.3 mg, sodium starch glycolate - 7.2 mg, talc - 3 mg; hypromellose - 6.6 mg), lake of quinoline yellow - 0.5 mg, polyethylene glycol 400 - 0.33 mg, titanium dioxide - 1.48 mg was prepared by homogeneous mixing in a mortar. 10 mg of placebo was placed in a 50 mL volumetric flask and its extract was prepared as described under "Procedure for Tablet." 1.00 mL of the extract was subject to analysis following the general procedure.

Results and discussions

Scheme in Fig. 2 showed a general overview of the oxidation of Protionamide by potassium peroxomonosulfate. Protionamide was oxidized rapidly to Protionamide sulfoxide, after which it was oxidized further to the final product, 2-Propylisonicotinamide. The reaction products shown in the scheme were obtained by the method of preparative chemistry. The structures of all these compounds were established on the basis of spectral data and the results of elemental analysis.

Prothionamide exhibited intense absorbance around 288 nm, while prothionamide sulfoxide shows the absorption maximum at 380 nm.The 380 nm wavelength was chosen to monitoring reaction. $KHSO_5$ showed no absorbance in the UV/Vis region and thus did not interfere with any UV/Vis measurements (Fig. 3).

A data from the UV/Vis instrument showed a bistage reaction, with a rapid initial oxidation of Protionamide, which took less than 10 seconds. This was followed by the slow decomposition of the Protionamide sulfoxide product, to 2-propylisonicotinamide, which was the byproduct of further oxidation. Absorbance at time 0 s for a given concentration of prothionamide in the presence of an excess of oxidant was determined by extrapolation of the descending kinetic curve of the second stage of the reaction of the slow decomposition product of the sulfoxide of prothionamide to 2-propylisonicotinamide (Fig. 4).

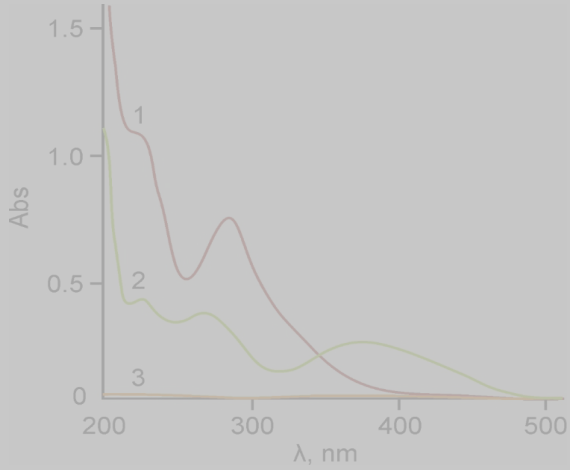

Fig. 3. Spectra of PTA (1), PTA-SO (2), $KHSO_5$ (3); c(PTA) = 5.0×10^{-5} M, (2) c(PTA-SO) = 5.0×10^{-5} M, c($KHSO_5$) = 5.0×10^{-5} M.

The extinction coefficient for Protionamide sulfoxide was calculated. Linear regression performed on the data set showed a slope, which was equal to the extinction coefficient, in this case 4920± 429 M^{-1} cm^{-1}.

Effect of HCl concentration was investigated in the range from 0.006–0.5 M. As is seen from the results (Table 1) there is the reverse dependence between the absorbance values HCl concentration. The absorbance maximum is observed at lower values of HCl concentration.

Stoichiometry. The stoichiometry of this reaction was very complex and depended on the ratios of the oxidant to the reductant. In excess Protionamide a 1:1 stoichiometric ratio was quickly established in which there appeared to be a quick and facile oxygen atom transfer from the $KHSO_5$ to Protionamide. The establishment of this stoichiometry was almost instantaneous.

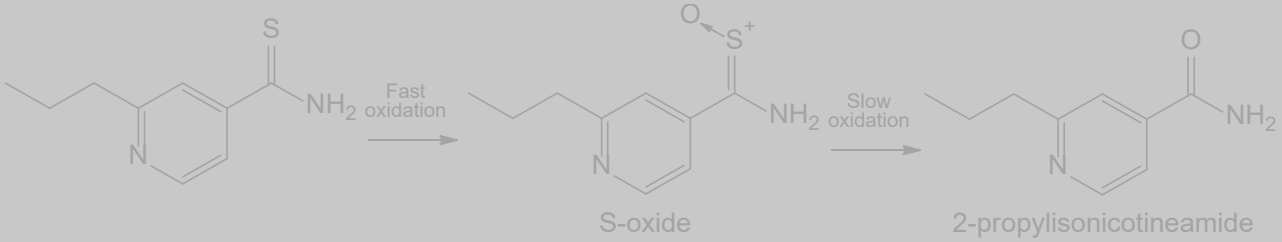

Fig. 2. General reaction overview.

The proposed method is indirect and essentially based on the determination of PTA-SO released *in situ* upon reacting PTA with $KHSO_5$ in acid medium. The determined concentration of the PTA-SO is related to the concentration of the drug responsible.

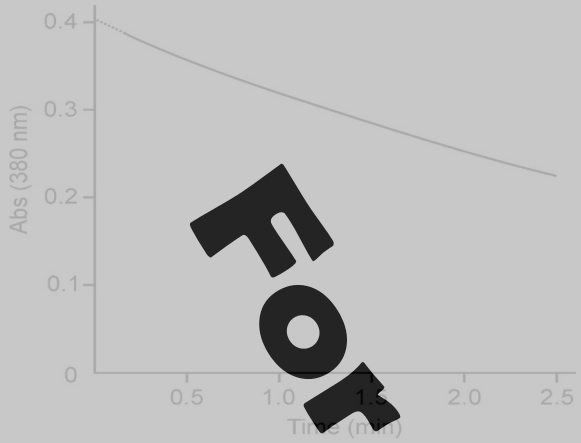

Fig. 4. Decomposition of PTA-SO over 2,5 min. c(PTA) = 1.0×10^{-4} M, c(HCl) = 6.0×10^{-3} M, c($KHSO_5$) = 0.005 M.

Table 1. Effect of HCl concentration on absorbance of PTA-SO [PTF] = 1×10^{-4} M; [$KHSO_5$] = 5×10^{-3} M.

c(HCl), M	A_{380}
0.006	0.492
0.10	0.490
0.25	0.488
0.50	0.485

Preliminary experiments were performed to determine the optimum concentration of $KHSO_5$ and HCl to give the maximum response. 6.25 mL of 0.7% aqueous solution of $KHSO_5$ was found optimum in the method, and 3.00 mL 0.05 M HCl was found ideally suited to prepare the drug solution and no additional acid was required to cause the redox reaction that facilitated the assay. The redox reaction between PTA and $KHSO_5$ was instantaneous. As the acid concentration was increased, so was the protonation state of the sulfur center, which reduced the nucleophilicity, and thus the electrophilic attack of oxygen from $KHSO_5$ was less likely. The resulting molecule would then also be resonance stabilized, as indicated in Scheme Fig. 5, below.

Method Validation

Linearity and sensitivity

The calibration graphs obtained follow Beer's law up to 45 μg mL^{-1} PTA. Regression parameters along with the respective dynamic linear range and the detection and quantification limits are given in Table 2.

Table 2. Summary of the UV method validation.

Parameters	UV-method
Working λ_{max}	380 nm
Calibration range	5–45 μg mL^{-1}
Regression equation	y = 0.0269x
Regression coefficient (r^2)	0.999
SD of slope	0.0000495
SD of intercept	0.00136
LOD, μg mL^{-1}	0.17
LOQ, μg mL^{-1}	0.51

5 Point calibration curve data was constructed in the range of 5 to 45 μg mL^{-1}, where the Beer's law was obeyed. The correlation coefficient was found 0.999, which is within the limit. The limit of detection (LOD) and limit of quantification (LOQ) for Prothionamide is found to be 0.17 μg mL^{-1} and 0.5 respectively, indicating that the proposed UV method is highly sensitive.

Precision and Accuracy. The accuracy and precision of the method were assessed by repeated analyses of a pure solution of the drug at three concentration levels within the linear range. The percentage recovery ranged from 98.40±1.13 to 99.11±0.79 (n = 3) with a relative standard deviation of no more than 1.13%, while its value found by the standard pharmacopoeial method given in the quality certificate (μ) was 98.9% (Table 3). The fulfillment of the inequality $|(\bar{x}-\mu)100\% / \mu| < t\alpha(0.95, n=3)\times RSD/\sqrt{n}$ indicates the absence of systematic error and the reliability of the results obtained.

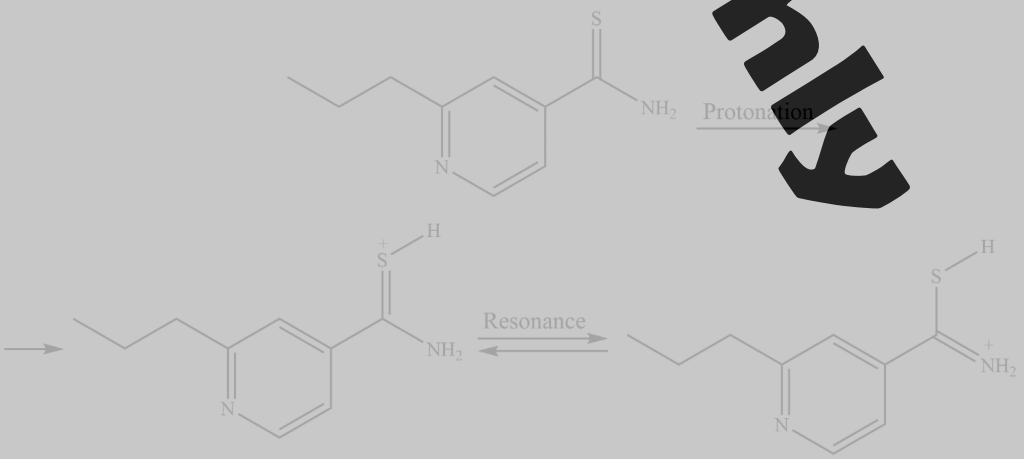

Fig. 5. Protonation scheme.

Selectivity. The selectivity of the proposed methods was checked using laboratory prepared mixtures. They were successfully applied to the analysis of the pharmaceutical formulation PTA with no interference from other dosage form additives.

The placebo blank when subjected to analysis by the proposed method yielded absorbance value close to those of the reagent blank (see Fig. 3).

Table 3. Estimation of Prothionamide in the pure drug solution.

Amount taken (μg mL^{-1})	Amount found (μg mL^{-1})	Recovery ± RSD, % (*n*=3)	δ*,%
10	9.84±0.28	98.40±1.13	– 0.5
15	14.87±0.29	99.11±0.79	+0.2
20	19.77±0.90	98.87±0.77	– 0.05

RSD = Relative standard deviation, % Re = Recovery, *n* = number of independent replicates (number of reportable values). δ*= ($\bar{x}$-μ)100% / μ . μ - quantification data, given in the Certificate of Quality.

Analysis of tablet formulations

On analyzing of Prothionamide in tablet formulation using proposed method, the percent recoveries were 98.57±1.39 to 99.03 ±1.17 (*n* = 3) with relative standard deviation not more than < 1.41%, while its value found by the standard pharmacopoeial method given in the quality certificate was 99.0% (μ =247.5 mg/tabl.) (Table 4). The reliability of the obtained measurement results is proven by comparing the accepted reference value (μ) with the level of results of the proposed method:

$|(\bar{x}-\mu)100\% / \mu| < t_{\alpha}(0.95, n=3)\times RSD/\sqrt{n}$.

To further establish the accuracy and reliability of the proposed method, recovery experiment through standard-addition procedure was performed. To the preanalyzed tablets powder, pure PTA was added at three levels and the total was found by the proposed method. Each determination was performed in triplicate. From the percent recovery values of pure drug, added to the tablet powder, summarized in Table 5, it is clear that coformulated substances in the tablets did not interfere in the determination, and thereby complementing the results of the selectivity study. $|(\bar{x}-\mu)100\% / \mu| < t_{\alpha}(0.95, n=3)\times RSD/\sqrt{n}$.

Table 4. Estimation of Prothionamide in tablet formulations.

Label claim (mg/tab)	Conc. prepared (μg mL^{-1})	Conc. recovered (μg mL^{-1})	Amount found (mg/tab)	% Label claim	Mean ± SD (*n*=3)	% RSD
250 (247.5)*	10	9.82	245.5	98.2	98.57±1.39	1.41
		9.74	243.5	97.4		
		10.01	250.25	100.1		
	15	14.82	247.0	98.8	99.03 ±1.17	1.18
		15.05	250.8	100.3		
		14.70	245.0	98.0		
	20	19.65	245.6	98.25	98.95 ±0.79	0.79
		19.76	247.0	98.8		
		19.96	249.5	99.8		

* μ - quantification data, given in the Certificate of Quality. SD = Standard deviation, RSD = Relative standard deviation, *n* = number of independent replicates.

Table 5. Recovery studies on marketed formulation by the method of additives.

Conc. level	Formulation (μg mL^{-1})	Amount added (μg mL^{-1}), μ	Abs.	Amount recovered, $\bar{x}$	Recovery, %	Mean % recovered ± SD (n=3)	RSD	Relative error (% R)
80%	0.8 ml of 500 μg/mL (16.00)	0.2 ml of 500 μg/mL (4.00)	0.534	3.96	99.0	98.17 ± 0.76	0.78	- 1.8%
			0.532	3.92	98.0			
			0.531	3.90	97.5			
100%	1.0 ml of 500 μg/mL (20.00)	0.25 mL of 500 μg/mL (5.00)	0.665	4.88	97.6	98.33 ± 0.70	0.71	- 1.7%
			0.674	4.95	99.0			
			0.667	4.92	98.4			
120%	1.2 ml of 500 μg/mL (24.00)	0.5 mL of 500 μg/mL (10.00)	0.905	9.75	97.5	98.63 ± 1.03	1.04	- 1.4%
			0.911	9.95	99.5			
			0.909	9.89	98.9			

Therefore, the standard error and standard deviation obtained for prothionamide were satisfactorily low. The results obtained by the proposed method were statistically compared with the standard pharmacopoeial method, and there was no significant difference between them in terms of both accuracy and precision; which indicates the possibility of using the proposed method for routine analysis of medicinal products.

Conclusions

A relatively simple, rapid, accurate and precise UV spectrophotometric method has been developed and validated for the analysis of prothionamide in active pharmaceutical ingredients (APIs) and tablet dosage forms. The results demonstrated the usefulness of potassium peroxomonosulfate as a reagent for the spectrophotometric assay of Protionamide in pharmaceuticals.

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